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13. ABSTRACT *(Maximum 200 words)*
To characterize skeletal muscle function in women during altitude exposure, 19 women (22±1 yr; mean±SE) with normal menstrual cycles were studied at sea level (SL, days 1, 5, and 9 of the follicular *and* luteal phases) and after 1, 5 and 9 days of continued exposure to 4300 m (days 2, 6 and 9-10 of the follicular *or* luteal phase). Maximal voluntary contraction force was measured before ("strength"") and every min during intermittent static contraction exercise (50% of strength, 5 sec contraction/5 sec rest) of the adductor pollicis muscle and every 2 min during dynamic contraction exercise (18 ± 2% of strength at a contraction rate of 1Hz) of the quadriceps femoris muscle, to exhaustion. Major findings were: 1. strength and time to exhaustion did not vary significantly ($P > 0.05$) between menstrual phases or among days within each phase at SL or altitude, and 2. endurance time to exhaustion for women --- in sharp contrast to male historical controls --- was similar at altitude as at SL. (Men have a much greater reduction in endurance time). The gender difference in muscle endurance was independent of menstrual phase and remained despite men and women having identical levels of strength and exercising to exhaustion at a similar work rate.

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EXECUTIVE SUMMARY

In high terrestrial altitude (mountain) environments, endurance during activities involving large muscle groups (e.g., marching, running, climbing) is degraded due, in part, to the effect of lower oxygen content of the ambient air on skeletal muscle. The precise mechanisms of the altitude-induced acceleration in skeletal muscle fatigue are not well understood. Previous data from our laboratory suggested that women experience less of a decrement in small muscle endurance at altitude than men, and that this effect might be related to cyclic changes in the hormonal milieu associated with the menstrual cycle. To characterize skeletal muscle function in women during acute and prolonged exposure to high altitude, nineteen healthy women (22±1 yr; mean±SE) with normal menstrual cycles were studied at sea level (during days 1, 5, and 9 of the both follicular ***and*** luteal phases) and after 1, 5 and 9 days of exposure to 4300 m altitude at Pikes Peak, CO (during days 2, 6 and 9 or 10 of either their follicular *or* luteal phase). Maximal voluntary contraction (MVC; "strength") force was measured before (initial strength) and every min during submaximal intermittent static contraction exercise (50% of initial strength, 5 sec contraction/5 sec rest) of the adductor pollicis muscle and every 2 min during submaximal dynamic contraction exercise ($18 \pm 2\%$ of initial strength at a contraction rate of 1Hz) of the quadriceps femoris muscle, to exhaustion. For both exercise modes, the major findings of this study were: 1. initial strength and time to exhaustion did not vary significantly ($P > 0.05$) between menstrual cycle phases or among days within each cycle phase, 2. initial strength was maintained at altitude, and 3. endurance time to exhaustion was similar at altitude as at sea level. The lack of a decrement in endurance time at altitude in these women is in sharp contrast to male historical controls, who showed a reduction in endurance time. The gender difference in muscle endurance was not attributable to differences in initial strength or work rate and was independent of menstrual cycle phase. More research is necessary to define the precise mechanism(s) responsible for the difference in muscle endurance performance between men and women during altitude exposure.

INTRODUCTION

I. Overview

Women currently comprise approximately 15% of the active duty personnel in the US Army. In addition, there is increasing participation of women in numerous military tasks requiring intense or prolonged fatiguing physical effort that traditionally were reserved for men. Yet, while work and exercise performances of men have been studied over a wide range of activities of varying intensities and durations in different environments, there is little comparable information available for women. Thus, many aspects of the work and exercise performance capabilities of women in the military remain poorly defined.

II. Exercise Performance and the Menstrual Cycle

Exercise performance is dependent on complex interactions between the muscular, cardiovascular, respiratory, metabolic, neural and hormonal systems of the body (2,4,7, 15,21,38, 46,51, 66,68,78). The cyclical changes of hormonal concentrations of estrogen and progesterone throughout a menstrual cycle have many specific, interactive, and sometimes opposing physiological actions with potential impact on the exercising female (43). Briefly, estrogen and progesterone enhance muscle glycogen storage (33) and repletion (53) with estradiol also promoting lipolysis and lipid synthesis (8,11). The shift in metabolism towards free fatty acids leads to a decrease in glycogenolysis and gluconeogenesis (11), and possibly improved endurance performance (22,36). In contrast, a high progesterone level during the luteal phase stimulates ventilation and the ventilatory responses to hypoxia and hypercapnia (69), which may cause a performance decrement owing to a subjective feeling of dyspnea in untrained females, but may, enhance exercise performance in some situations (e.g., during altitude exposure) by improving

arterial oxygen saturation and oxygen delivery. Moreover, a greater urinary protein loss during the luteal phase consistent with a greater protein catabolism (40) may (80) or may not (17,34,61) be associated with a loss of muscle strength. Hormone-induced changes in blood flow to muscle tissue mediated via ovarian steroid receptors on vascular smooth muscle (72) may impact on oxygen and substrate delivery, and on "flushing" out of metabolic end products linked with muscle fatigue (46,77). Ovarian steroids may also affect the central nervous system or neural transmission (which have been demonstrated in animal models (52)) to improve muscle function. Consideration of the variations in estrogen and/or progesterone levels and the complexity of the interactions with numerous physiological systems makes it is difficult to predict how exercise performance will be altered throughout the menstrual cycle. In addition, because changes in exercise performance throughout a menstrual cycle may be subtle, their detection may not always be possible.

Indeed, previous reports indicate that maximal and submaximal aerobic exercise performances during exercise utilizing large muscle groups (e.g., running, cycling, or swimming) may change (34,36,44,53,62,69) or not change (16,18,60,61,69,73) as a consequence of menstrual cycle phase. Of the studies reporting improved aerobic exercise performance, the improvement typically (34,36,53,62) though not always (44,69) occurred in the luteal phase and either was (34,36,44) or was not (44,61) linked with favorable changes in factors often associated with altered performance (e.g., ratings of perceived exertion, cardiac output, blood lactate levels, and anaerobic threshold). Interestingly, in many instances factors were altered even when no changes in maximal and submaximal aerobic exercise performance could be detected between phases (5,18,73). Moreover, for some investigations that utilized multiple performance indexes

(e.g., strength and endurance measures) of different sized muscle groups or multiple exercise intensities for a given performance index, the exercise responses were altered for some, but not all, performance indexes or exercise intensities in the follicular or luteal phase (34,36,44,69). It is interesting that *of the studies showing changes in exercise performance between the follicular and luteal phases*, large muscle group endurance exercise typically improved during the luteal phase (34,36,53,62), isolated smaller muscle endurance declined during the luteal phase (57) or at mid-cycle (67), and muscle strength improved during the follicular phase and mid-cycle (14,58,59,80). Collectively, such inconsistent and seemingly random distribution of exercise findings among studies for specific menstrual cycle phases make it difficult to determine if cyclic changes in estrogen/progesterone concentrations throughout the menstrual cycle truly alter exercise performance, or alter various performance indexes differently within a phase. It could be that part of the inability to consistently detect differences in exercise performance attributable to variations in ovarian hormone concentrations --- if they truly exist --- may relate to varying sources of experimental variability among studies. While not all known experimental variability can be controlled (e.g., inter- and intra-subject menstrual cycle length variability), many other potential sources can be minimized (e.g., proper exercise model used for testing (29,35,39)).

III. Exercise Performance and Altitude Exposure

The ability to perform tasks requiring physical exertion is an essential component of most military operations (55), and factors or conditions which degrade physical performance can jeopardize the success of a military mission. Acute exposure to high terrestrial altitude (mountain) environments impairs exercise performance of activities involving large muscle groups (e.g., marching or running at the same absolute work rate as at sea level) in men and

women (23,24). With chronic altitude exposure and successful altitude acclimatization, large muscle group endurance exercise performance improves relative to acute altitude exposure, but does not fully recover to levels measured at sea level before the exposure (24,32,83).

To better understand impaired exercise performance at altitude, progressive muscle fatigue during exercise at altitude must be examined since skeletal muscle is, after all, the ultimate effector for physical work and exercise activities. While skeletal muscle fatigue has been studied frequently at altitude (primarily in men) (10,12,20, 25,28,37, 74,82), the results have been contradictory. Accelerated (12,20,25,27,37), attenuated (10), or unaltered (12,20,37) rates of muscle fatigue during submaximal exercise at altitude have been reported. Contradictory findings of muscle fatigue at altitude may relate to 1. Inappropriate use of sustained static muscle contraction as the fatigue model. (A sustained static muscle contraction exercise model (12,20,28,37,82) causes ischemia in the active muscles (71) due to intramuscular pressure exceeding perfusion pressure and, therefore, tends to limit differences between sea level and altitude regarding local factors normally associated with muscle fatigability (46,71)); 2. The considerable variation in work performed by a given muscle during conventional, dynamic exercise modes (treadmill exercise or stationary cycling are the methods usually employed in testing (45)); 3. Lack of distinction between muscle fatigue and exhaustion (10,12,26, 28,37); and/or 4. various durations of exposure to altitude prior to testing (12,25, 28,37).

Because virtually all research studies of muscle fatigue at altitude have been conducted using only men, interpretation of the results and the applicability of the findings to women are limited. In addition, no systematic study has been devoted to the potential influences of changes in ovarian hormone levels on skeletal muscle fatigue during short-term and prolonged altitude

exposure to altitude. Since skeletal muscle function is the result of a complex interaction of the intrinsic force-generating capacity of the muscle tissue itself, neural stimulation to the muscle and muscle tissue metabolism, changes in hormone levels during the menstrual cycle could affect any or all of these processes. None of these possibilities has been adequately studied at altitude, but limited data suggest that measurable differences in muscle strength and fatiguability between menstrual cycle phases has occurred in some (57,59,67) though not all (17,31) studies at sea level.

IV. Gender Differences Affecting Exercise Performance

In comparison to men, women are generally smaller in size (48) and, as a result, also have less muscle mass (48,50), strength (42,48,50), blood volume (3,19,65), lung volume (13), cardiac output (3,64,65) and a lower maximal oxygen uptake (4,22,76). During submaximal exercise that requires an *absolute* power output be maintained for a sustained period of time, endurance performance for women compared to men is likely to be poorer because women must necessarily exercise at higher percentages of their maximal strength and oxygen uptake (55) at sea level and altitude (i.e., the *relative* intensity of the submaximal exercise will be greater for women than men). In contrast, the exercise performance of women compared to men at sea level has been reported to be superior (22,47,50,57,79) when power output is reduced so that the women exercise at the same *relative* exercise intensity as men. Better endurance performance of women compared to men exists despite men and women being matched on muscle cross-sectional area (48), daily activity or training level (50,54,75), relative percentage of maximal force used during exercise (47,50,79), composition of dietary intake (75), and age (57). Whether endurance performance superiority at the same relative intensity is maintained for women compared to men at altitude is unknown.

The greater relative endurance performance of women compared to men has been proposed to involve a lower glycolytic to beta-oxidative potential in skeletal muscle (30,54), a decreased rate of muscle glycogen utilization (54), or a larger proportion of a given volume of active muscle occupied by slow-twitch, fatigue-resistant fibers (due to women having a smaller fast-twitch cross-sectional area (54). Thus, not accounting for dimensional and associated functional factors as well as cyclic changes in the hormonal milieu associated with the menstrual cycle (41,81) that may also affect performance (57,59,67) makes it difficult to determine if a difference in exercise performance at sea level or altitude is due to dissimilar relative exercise intensity or gender *per se.*

V. Exercise Model Selection

From the above discussions it is clear that the exercise model(s) used to detect potential exercise performance differences that may be associated with cyclic changes in estrogen/progesterone, altitude exposure and gender differences should include: 1. an ability to be used repeatedly within and between each phase of a menstrual cycle, 2. relatively minor intra-individual test-retest variability, 3. sensitivity to experimental interventions, and 4. multiple, quantifiable performance indexes (e.g., muscle strength and muscle endurance) during each exercise test (25,26,45). In addition, the exercise model should allow direct comparison between men and women.

Two exercise performance models that fulfill these requirements have proven to be ideal for the study of muscle and exercise performance. These are the adductor pollicis intermittent static contraction exercise model (25) and the quadriceps femoris dynamic contraction exercise model (26,27). The adductor pollicis exercise model uses high force, intermittent static

contractions of a single small muscle thereby allowing quantification of a progressive decline in muscle strength resulting from submaximal static contractions. But because power output of muscular exercise is determined by not only the static strength of muscles, but also by their speed of movement, the quadriceps femoris exercise model, which uses lower force, dynamic contractions of a large muscle synergy, provides a means to quantitate progressive muscle fatigue in terms of declines in both static muscle strength and contraction velocity (27). The adductor pollicis muscle consists predominately of slow-twitch muscle fibers (63), and the quadriceps femoris muscle consists of nearly equal proportions of slow and fast-twitch muscle fibers (54). The use of isolated muscle group exercise models also eliminates many of the extraneous variables (e.g., central circulatory limitation) associated with the use of conventional ergometric procedures and that may impact on local muscle function. Thus, the benefits afforded by using concomitantly these models in the same subjects are: 1. potential changes in maximal and submaximal exercise performance can be evaluated before and during different exhausting activities using two exercise models having minimal test-retest performance variability, 2. differences in force levels (high vs low) and type of contraction (static vs dynamic), muscle size (small vs large), and muscle fiber composition (predominately slow-twitch vs mixed). Inherently different exercise models used under the same experimental conditions may therefore allow resolution of some previous contradictory observations reported in the literature.

In addition, both of these exercise models can be used repeatedly to assess multiple indexes of exercise performance within and between menstrual cycle phases. This allows for the determination of the effects of acute alterations in ovarian hormone concentrations on exercise performance at sea level and altitude. Because altitude studies using these exercise models have

been conducted by the same investigative team under similar experimental conditions using men (25,27), direct gender comparisons of the exercise performance indexes can also be performed.

VI. Study Purpose and Hypotheses

The purpose of this study was to characterize skeletal muscle fatigue in premenopausal women with normal menstrual cycles during acute and prolonged exposure to high terrestrial altitude. The experimental design allowed skeletal muscle strength and endurance time to exhaustion to be measured repeatedly during the follicular and luteal phases at sea level and altitude using an intermittent static contraction exercise model (to study adductor pollicis muscle fatigue) and a dynamic contraction exercise model (to study quadriceps femoris muscle fatigue). The experimental design also allowed muscle function in women to be compared to that of men at sea level and altitude (25,27).

The main hypotheses of the study were: 1. muscle strength and endurance would differ between menstrual cycle phases and among days within a phase at sea level and altitude, 2. muscle strength and endurance would be impaired in response to altitude exposure, and 3. the sea level to altitude strength and endurance responses of women would differ from those of male historical controls.

BODY

I. EXPERIMENTAL METHODS

A. Subjects

Nineteen healthy, eumenorrhic women gave their informed written consent to be test subjects. All were sea-level residents who had not resided at altitudes greater than 1,500 m, and had no history of oral contraceptive use or pregnancy in the year preceding the study. The mean

(± SE) age, height, and weight of the subjects were 22.3 ± 1.0 yr, 167.9 ± 1.0 cm, and 64.1 ± 2 kg, respectively. As a group, they were physically active, but not endurance trained (conventional bicycle ergometer maximal oxygen consumption measured at sea level averaged 42.5 ± 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$).

B. Study Locations

Sea level testing took place in the Geriatric Research Education and Clinical Center of the Palo Alto Veterans Administration Medical Center, Palo Alto, CA (altitude:30 m). Altitude testing was conducted at the US Army Research Institute of Environmental Medicine Pikes Peak Laboratory Facility on the summit of Pikes Peak, CO (altitude: 4350 m). Testing at sea level preceded testing at altitude with at least one month intervening between testing at each location. After traveling to Pikes Peak from California in less than six hours via airplane and automobile, the test subjects remained on the summit continuously for 12 days. Ambient temperature was comfortably maintained (range: 20 to 23 ^{0}C) at each location.

C. General Experimental Design and Procedures

To ensure familiarization with all equipment, personnel, and procedures and to learn to execute intermittent static contractions exclusively with the adductor pollicis muscle and dynamic knee extension exclusively with the quadriceps femoris muscles of one leg, subjects were scheduled to undergo at least one to two preliminary adductor pollicis exercise testing sessions and two to three preliminary knee extension exercise testing sessions at Palo Alto, CA. prior to the definitive test sessions. Preliminary sessions consisted of practicing repeated submaximal static and/or dynamic contractions interspersed with periodic maximal contractions.

Based upon menstrual cycle history, menstrual diary, and serum hormone levels,

definitive tests were conducted at sea level on days 1, 5, and 9 following both the onset of menses (day 0, follicular phase) and detection of the luteinizing hormone (LH) surge (day 0, luteal phase). The sequence of the follicular and luteal phase definitive test sessions at sea level was balanced among subjects; approximately half started testing in their follicular phase and the other half started testing in their luteal phase. The second sea-level test session (i.e., the remaining menstrual cycle phase) was begun in the next consecutive menstrual cycle and not within the same menstrual cycle. Subjects were then randomly assigned to either the follicular or the luteal phase group for the altitude exposure to be tested on days 2 (travel to altitude occurred on day 1 of each phase), 6, and 9-10 of the follicular or luteal phase (which were the 1st, 5th and 9th days of altitude exposure). In other words, definitive adductor pollicis and quadriceps femoris testing sessions were scheduled for each women at sea level during her follicular and luteal phases but at altitude only during one phase.

Exercise test days were planned to correspond with theoretical changes in the serum concentrations of the ovarian hormones to determine if estradiol and progesterone --- in varying combinations --- alter muscle performance at sea level and during acclimatization to altitude. Exercise test day one or two of each phase corresponds to the lowest ovarian steroid levels. Test day five is typically associated with the highest estradiol and progesterone levels during the luteal phase and with rising estradiol and very low progesterone levels during the follicular phase. Test day nine or 10 typically corresponds with high estradiol and low progesterone levels in the follicular phase, and with similarly high estradiol, but also high progesterone levels in the luteal phase.

1. Subject Participation Problems

Due to unavoidable time constraints and scheduling conflicts imposed by a companion investigation of the effects of high altitude on water/fuel metabolism and fluid/energy balance, as well as lack of subject availability due to recruitment and attrition problems, and their conflicting personal commitments, menstrual cycle duration irregularities, and/or pre-existing orthopedic problems in the thumb or knee joint, not all subjects were able to participate in all of the testing sessions. For example, one-leg peak oxygen uptake tests, scheduled to be performed during the second or third preliminary exercise testing session and which were required to determine the relative exercise intensity level of submaximal knee extension, were completed on only six of the 19 test subjects. Data presented within this report include only those subjects with complete definitive test data in at least one menstrual cycle phase at sea level or altitude.

2. Menstrual Cycle Phase Assessment and Hormone Measurements

Each subject, upon admission to the study (range three months to three weeks prior to initial sea-level measurements) kept a menstrual cycle diary, noting the date and duration of menses, the date of a LH surge, and duration of the cycle. Based upon a three-month history documented by diary or by information provided from the subject on cycle length, each subject began testing for her LH surge using an ovulation predictor kit (OvuQuick,Becton-Dickson, Rutherford, NJ) at least four days prior to the estimated time of her LH surge. Ovarian steroid hormones were measured on days 3 and 10 at sea level during the follicular and the luteal phase and on days 3, 6, 9, and 10 at altitude.

Blood for analyses of ovarian steroid hormones was obtained by venipuncture, allowed to clot for 30 min, then centrifuged at 3000 RPM for 10 min. The serum was immediately frozen at

-70 ^{0}C at sea level, and in liquid nitrogen at high altitude. All samples were analyzed at the same time, one month after the completion of the altitude studies. Serum aliquots were assayed for estradiol and progesterone by the General Clinical Research Center Laboratory at the University of Colorado Health Sciences Center. Estradiol and progesterone concentrations were measured using the Diagnostic Products Corporation (DPC) "Coat-A-Count" radioimmunoassay. For estradiol, the RIA sensitivity was 8 pg$\bullet$ml^{-1} and the test was linear up to the highest standard concentration (~3600 pg$\bullet$ml^{-1}). Within- and between-day precision (coefficients of variation) were 6% and 10.9%, respectively. For progesterone, the sensitivity was 0.2 ng$\bullet$ml^{-1} and the within- and between-day precisions were 7.6% and 11.9%, respectively. Four standards were used for each assay: a low, a high and two intermediates.

3. Device and Procedure for Studying Adductor Pollicis Muscle Fatigue During Intermittent Static Contraction Exercise

Exercise tests were performed using an experimental setup that permitted static contractions totally isolated to the adductor pollicis muscle (25,49). The right hand and arm of the subject were secured in supination with the fingers flexed and thumb abducted. A transducer (model SSM-250, Interface, Scottsdale, AZ; sensitivity 1.5 mV$\bullet$kg^{-1}), interfaced in parallel to an amplifier (model 13-421202, Gould, Cleveland OH; 90% response time in 2 ms), chart recorder (model 2200, Gould), and oscilloscope, was attached by an inextensible strap looped around the interphalangeal joint of the right thumb. Subjects had visual contact with the tracings on the oscilloscope at all times to provide them with feedback for maintaining the correct force of contraction during submaximal exercise.

a. Determination of MVC force.

After the subject was seated and the hand and thumb were properly oriented and secured, three baseline maximal voluntary contractions (MVC) lasting three to five sec were obtained. There was at least a one min rest between each MVC. The value of the highest MVC ("strength" or rested MVC force) was used to set the submaximal exercise target value.

b. Submaximal intermittent exercise.

Submaximal exercise consisted of intermittent 5 sec static muscle contractions at 50% of rested preexercise MVC followed by 5 sec of rest (i.e., duty cycle = 0.5). Subjects were verbally instructed to start and stop contractions by an investigator timing the events. At the end of every min (or every 6th submaximal contraction), a MVC was performed for the full 5 sec instead of the target force contraction. The exercise session ended when the target value (50% MVC) could not be maintained for 5 sec or MVC fell to or below the target value ("exhaustion") (see **FIGURE 1**).

4. Device and Procedure for Studying Quadriceps Femoris Muscle Fatigue During Dynamic Contraction Exercise

The specially-designed device for performing 1-leg dynamic knee extension exercise interspersed with maximal static 1-leg knee extension contractions has been described in detail (26). Briefly, it consists of a platform on which the subject sits, an attached minimal-friction weight-pulley system with an ankle harness, transducers for measurement of force and ankle displacement during dynamic knee extension and separate force transducers for measurement of force of static knee extension MVC. In order to precisely control work rate, two vertical columns of 14 light crystal diodes (LCDs) are placed in front of the subject. The right LCD column is

wired in series to the position transducer (Celesco Transducer Products Inc., Canoga Park, CA, Model PT101-0100-111-1110) such that the number of LCDs lighted is proportional to ankle displacement during knee extension. The left LCD column is connected to a synthesizer/function generator which automatically and sequentially lights from one (at the 90^0 knee angle starting position) to 14 (corresponding to ankle displacement on reaching 150^0 of knee extension) to one (return to 90^0 starting position) at a pre-determined knee extension rate of 1 Hz. To maintain correct distance and rate of dynamic knee extension, the subject continuously matched the column of LCDs controlled by leg movement with that controlled by the synthesizer/function generator. The LCD units simplify subject and investigator monitoring of adherence to the required work rate. Because the knee extension movement encompasses 60^0 and there are 13 intervals between LCDs, the maximum allowable difference between the desired and actual knee extension angle is 4.62^0. Muscle exhaustion is defined as a mismatch of only one LCD between the right and left LCD columns for three consecutive knee extensions. This effectively means that exhaustion is associated with an inability to complete the last five degrees of knee extension contraction --- from 145^0 to 150^0 --- at the required contraction rate. Voltages proportional to force and ankle displacement was continuously recorded. Work rate (watts) was determined by multiplying mean force developed per contraction, distance of ankle movement during knee extension from 90^0 to 150^0 and rate of knee extension (1 Hz).

To measure the decline in force generating capacity and rate of muscle fatigue, the exercise device allowed performance of MVCs of the knee extensor muscles during brief (≤ 5 sec) pauses in dynamic knee extension. This procedure involved rapid disconnection of the ankle harness from the weight-pulley system, connection to a force transducer dedicated to

measurement of MVC force, actual measurement of MVC force, and reconnection to the weight-pulley system.

a. Determination of MVC force. On each day of definitive testing, the subjects performed three or more practice knee extensor MVCs with each leg. Each practice MVC was followed by at least one min of rest. MVC force ("strength" or rested MVC force) of the leg used for dynamic exercise (the active right leg) was then measured immediately prior to, at the end of every two min during and immediately following dynamic knee extension. MVC force of the leg resting during dynamic exercise (the inactive left leg) was measured shortly before dynamic knee extension of the active right leg and within two sec after completion of exercise of the right leg. Each MVC lasted two to three sec. A knee angle of 90^0 was used.

b. Submaximal constant work rate knee extension exercise. For each subject, 1-leg dynamic knee extension at a frequency of 1 Hz was performed to exhaustion at the same constant work rate (18 ± 2 watts) under sea level and altitude conditions. The time course of fatigue was determined from MVC force measurements during pauses of ≤ 5 sec at the end of every two min of exercise and immediately post-exercise. (See **FIGURE 2**).

c. Respiratory gas exchange. Minute ventilation, oxygen uptake, carbon dioxide production and respiratory exchange ratio were monitored continuously at rest and throughout each knee extension exercise session using a Sensormedics Metabolic Measurement Cart (Model 2900). Prior to each test, the metabolic cart was calibrated with certified gases.

d. Arterial oxygen saturation, heart rate, perceived exertion. Continuous measurement of the arterial oxygen saturation of fingertip blood was performed

noninvasively using a SensorMedics finger oximeter (SensorMedics Corp., Anaheim, CA, Model 763320-101). Heart rate was determined from continuous electrocardiographic or finger oximeter recordings at rest and during exercise. Every two min during dynamic exercise, subjects rated their perceived exertion localized to the active muscles using the 6 to 20 category rating scale developed by Borg (9).

e. Electromyographic measurements (EMG). Surface EMG recordings from electrodes placed cutaneously over the bellies of three of the quadriceps femoris muscles, i.e., vastus lateralis, vastus medialis, and rectus femoris were acquired during dynamic knee extension and MVC. To minimize day-to-day variation in electrode placement, electrode sites were measured and marked daily with indelible ink. EMG signals were collected for 12 sec every two min of dynamic knee extension. Each specific recording period encompassed two to four sec of dynamic knee extension prior to MVC, three to five sec of static knee extension for measurement of MVC, and two to four sec of dynamic knee extension after each MVC. All recordings of EMG, and force and position transducer signals were collected simultaneously every two min at a rate of 1 KHz using the Noraxon Telemetry System Research Package (Noraxon USA, Scottsdale, AZ). The bandwidth used for collection of all EMG signals was 0 to 500 Hz. Each EMG signal during submaximal exercise and MVC was full-wave rectified and integrated. Previous studies of dynamic knee extension exercise have indicated minimal, non-quadriceps femoris muscle involvement (1,25). Complex EMG analyses on over 3,000 files have not yet been completed and will therefore not be discussed in this report. When the data analyses are completed, they will be discussed in a DOD Technical Report and/or the open scientific literature properly referenced to Defense Women's Health Research Program

(DWHRP) grant.

5. Statistical Comparisons and General Questions

The adductor pollicis and knee extension definitive exercise testing schedule is outlined in **Table 1**. The subjects who participated varied considerably both within and between the adductor pollicis and quadriceps femoris exercise test comparisons, the number of subjects in the follicular and luteal phase varied among all comparisons, and only five of the 19 subjects completed all scheduled definitive sea level and altitude adductor pollicis and knee extension exercise tests. For these reasons, and to not further reduce statistical power by including only those subjects participating in all tests, separate repeated-measures analyses of variance, t-tests and/or regression analyses were conducted to answer the following general questions:

1. Does the effect of changes in ovarian hormones associated with the menstrual cycle affect adductor pollicis and quadriceps femoris muscle MVC force and endurance at sea level? (two-factor [menstrual phase, phase day]).

2. Does the effect of changes in ovarian hormones associated with the menstrual cycle affect adductor pollicis and quadriceps femoris MVC force and endurance upon exposure to high altitude and during subsequent altitude acclimatization? (three factor [altitude exposure, menstrual cycle phase, phase day]).

3. Do the sea level to altitude MVC force and endurance responses of women differ from those of men under similar experimental conditions during adductor pollicis testing (25) and quadriceps femoris testing (27)? (Two factor [gender, altitude exposure]).

If a significant main effect was identified during each analysis of variance, Tukey's multiple comparison procedure was used to assess the significance of specific differences in

mean values with respect to experimental conditions. For all analyses, a difference was accepted as significant if $P<0.05$. Data are presented as means ± SE, unless otherwise noted.

II. RESULTS

A. Ovarian Hormone Values. Values for estradiol and progesterone during the third and 10th day of the follicular and luteal phases at sea level and the third, sixth, ninth and 10th day at altitude are presented in **TABLE 2.** At sea level, estradiol and progesterone levels were higher ($P <0.05$) during the third and tenth days of the luteal phase compared to the same days of the follicular phase, respectively (primarily *intra*-subject comparisons). At altitude, levels of progesterone --- but not estradiol --- were higher ($P < 0.05$) for the luteal phase group than the follicular phase group for all days (*inter*-subject comparisons). Values for estradiol and progesterone for days three and 10 during the follicular or luteal phases, respectively, did not differ at altitude compared to sea level. Note the large magnitude of variability (as indicated by standard deviation) for estradiol and progesterone levels for each of the days.

B. Maximal and Submaximal Exercise Performance at Sea Level. Exercise performance data collected repeatedly from the same subjects under similar environmental conditions provide a "baseline framework" with which to determine if *intra*subject differences in ovarian hormone levels due to a difference in menstrual cycle phase affects muscle function.

1. *Adductor Pollicis.* Presented in **TABLE 3** are values for adductor pollicis maximal static voluntary contractile (MVC) force or "strength" and endurance time to exhaustion for 11 subjects who participated on days 1, 5, and 9 during both the follicular and luteal phases at sea level. For both the maximal and submaximal performance measures, there were no differences between phases or among days within a phase.

2. ***Quadriceps Femoris.*** Presented in **TABLE 4** are values for quadriceps femoris maximal static voluntary contractile (MVC) force (or "rested" MVC force) obtained just prior to the beginning of dynamic exercise, dynamic exercise endurance time to exhaustion, the percentage of rested MVC force used during dynamic exercise, percentage of remaining quadriceps rested MVC force at exhaustion, and steady-state oxygen uptake and heart rates for the seven subjects who participated on days 1, 5, and 9 during both the follicular and luteal phases at sea level. Rested MVC force, dynamic force, remaining MVC force, and oxygen uptake did not differ between phases or among days within a phase. Endurance time tended to be longer ($P = 0.07$) and heart rate tended ($P = 0.08$) to be higher during the luteal phase (heart rate during day one of the luteal phase was actually significantly higher than the heart rates for each of the testing days during the follicular phase).

C. Maximal and Submaximal Exercise Performance at Altitude. These exercise performance data allow insight in determining whether differences in ovarian hormone levels due to a difference in menstrual cycle phase affect muscle function during acclimatization to altitude.

1. ***Adductor Pollicis***. Presented in **TABLE 5** are values for adductor pollicis MVC force and endurance time to exhaustion for the follicular ($n = 8$) and luteal ($n = 5$) groups at sea level and altitude. Maximal static voluntary contractile force was consistent between groups, days, and upon exposure to altitude ($P > 0.05$ for all comparisons). Findings for endurance time to exhaustion, however, were less consistent and much more variable. For example, at sea level and altitude, submaximal performance for the follicular group tended ($P > 0.05$) to improve from days 1-2 through days 9-10 while submaximal performance for the luteal group tended ($P > 0.05$) increase among consecutive days at altitude, but not at sea level. There

were no statistically significant main effect differences between menstrual cycle phases or environment. The small sample sizes --- especially for the luteal phase group, however, precludes making a final conclusion as to whether differences in menstrual cycle phase affect intermittent static contraction muscle performance at altitude.

2. ***Quadriceps Femoris.*** Presented in **TABLE 6** are values for quadriceps femoris rested MVC force, remaining MVC force at exhaustion, and endurance time for the follicular (n=8) and luteal (n=3) groups at sea level and altitude. Rested MVC force was consistent between groups, days, and upon exposure to altitude ($P > 0.05$ for all comparisons). Findings for endurance time to exhaustion and rested MVC force remaining at exhaustion, however, were less consistent among days, especially at altitude. During the first day of altitude exposure compared to sea level, endurance time for both groups tended to decrease. But because of the inter-subject variability and the small number of test subjects in each group, neither the decline in endurance performance nor the recovery of endurance performance with continued altitude residence was statistically significantly different for either group ($P > 0.10$).

In **TABLE 7** are the percentage of rested MVC force used during dynamic exercise, and steady-state values for oxygen consumption, arterial oxygen saturation, and heart rate for the follicular and luteal groups at sea level and altitude. There were no statistically significant differences in percentage of rested MVC force or oxygen consumption either among days within a group or between groups. Arterial oxygen saturation was significantly reduced at altitude compared to sea level on each day within a phase and tended ($P > 0.05$) to increase for both groups with continued altitude exposure. There was no difference in arterial oxygen saturation between the follicular and luteal groups. Heart rate tended to increase at altitude compared to sea

level for each testing day, but a statistical increase was found only during the ninth or 10th day of testing in the follicular group.

Perceived exertion rose progressively throughout dynamic knee extension exercise and was always “19" or “20" at the point of exhaustion during each of the exercise sessions during the follicular and luteal phases at sea level and altitude (data not shown) indicating maximal effort. Similarly, there was no difference in inactive left leg MVC force measured just prior to and at the moment of exhaustion from dynamic exercise of the right leg during any of the exercise sessions (data also not shown). These findings support the view that muscle fatigue was not due to a general attenuation of central motor drive due to reduced subject motivation (27).

D. Maximal and Submaximal Exercise Performance of Women Compared to Men at Sea Level and Altitude.

1. ***Adductor Pollicis.*** To determine if maximal and submaximal small muscle performance of women differs from that of men during acute (one day) exposure to altitude, the eight women comprising the follicular group (first or second day following the onset of menses) were compared to exercise responses of eight men who had undergone identical experimental procedures (25). In **TABLE 8** are the rested MVC force and endurance times to exhaustion values for men and women. For both men and women, rested MVC force did not differ at altitude compared to sea level ($P > 0.05$). However, men were stronger than women at sea level and altitude ($P < 0.05$). Women had greater muscle endurance than men at sea level (approximately 2-fold) and altitude (approximately 3-fold) however. In addition, endurance time at altitude compared to sea level was decreased for men (mean -31%, $P < 0.05$) but not for women (mean +8%, $P > 0.05$).

The submaximal target force used was 50% of rested MVC force in both the previous study using men (25) and in the present study using women. While this *relative* target force was equivalent for men and women, the *absolute* force produced during each target force contraction was greater for the men because rested MVC force was greater. A greater absolute target force results in proportionally greater intramuscular pressure (70), and likely diminishes local blood flow and oxygen delivery. Therefore, the longer endurance times of women than men noted at sea level and altitude may relate to lesser strength (and target force) rather than a true gender difference in muscle endurance *per se*. To test this postulate, data of nine women in the current study were matched (P = 0.53) on sea level strength (i.e., rested MVC force) and target force to data of nine men previously studied (from ref. (25)). The data presented in **FIGURE 3** and **TABLE 9** clearly indicate that women have a longer endurance time to exhaustion than men at sea level when strength and target force are equivalent.

2. *Quadriceps Femoris.* Presented in **TABLE 10** are mean values of various performance indexes collected during knee extension exercise from women (n=11) in the present study compared to those previously obtained from men (n=8, (ref (27)). The group of 11 women used for comparison to men results from the combining the follicular (n = 8) and luteal (n = 3) groups. Data used are from the first day of their respective phase at sea level and altitude. There were no statistical significant differences between men and women with regard to rested MVC force, percentage of rested MVC used during dynamic exercise, work rate, oxygen uptake, and arterial oxygen saturation at sea level and altitude. Exercise heart rate was higher for women than men at sea level, but not at altitude. In addition, exercise heart rate increased from sea level to altitude for men but not women. Rested MVC remaining at exhaustion from dynamic knee

extension exercise was significantly higher for women than men at sea level and altitude ($P < 0.05$). Endurance time to exhaustion was longer for men than women at sea level ($P < 0.05$) but not altitude. In response to altitude exposure, endurance time to exhaustion was significantly reduced for men ($-49 \pm 7\%$, $P < 0.01$), but not for women ($-22 \pm 16\%$, $P = 0.08$). Because of the large intra-subject variability for endurance times to exhaustion in response to altitude exposure in men (range: -13% to -70%, median: -56%) and women (range: +100% to -74%, median: -32%), there was no statistically significant gender difference.

III. DISCUSSION

A. Sea Level Exercise Performance During The Menstrual Cycle

1. *Adductor Pollicis and Quadriceps Femoris Muscle Strength*

Muscle strength of the adductor pollicis muscle and the larger quadriceps femoris muscle was not affected by cyclic variations in the hormonal milieu associated with the menstrual cycle in the present study. This result suggests that the ability to provide voluntary maximal force during a single muscle contraction is not affected by acute estradiol elevations only (follicular phase) or in combination with elevated progesterone levels (luteal phase). There are few muscle strength studies with which to compare our findings, and the results of the ones that are available are often contradictory. Some (17,34,44,57,61) though not all (58,59,67) previous work are in agreement with our findings.

There had been some speculation that part of the reason for inconsistency among previous work related to the size of the muscle group or synergy tested; that it was more difficult for subjects to motivate themselves to provide maximal effort during large muscle contractions or activities compared to small muscle maximal contractions or activities (14), and the resulting

higher test-retest variability "masked" true, albeit small, ovarian hormone-induced changes in strength. Consistent with this belief were studies that utilized larger muscle group synergies (e.g., knee extensors, forearm, and hip extensors) (17,34,44,57,61) and showed no change in strength while those that used small muscles or muscle group synergies (58,59,67) reported changes in strength that were directly related to rising estrogen levels occurring within the follicular phase. (Note: Estrogen levels in the luteal phase were as high as, or higher than, during that of the follicular phase, yet force declined. This observation prompted some authors to postulate that progesterone was inhibitory to the effects of estrogen or caused muscle weakness (31)). However, results of other reports (14,31) that used larger muscles, a recent report (31) showing that women undergoing *in vitro* fertilization and who were tested during two phases of treatment --- during low and very high estrogen levels (controlled exogenously) --- had no significant strength increase in the small first dorsal interosseus muscle, as well as the data of the present study that compared strength of two vastly different sized muscles in the same subjects under similar experimental conditions, clearly indicate that differences in muscle size do not play a major role in the presence or absence of a significant change in strength throughout a menstrual cycle. The exact reason(s) for the discrepancies among studies remains unknown.

2. *Adductor Pollicis and Quadriceps Femoris Muscle Endurance*

The endurance time to exhaustion for adductor pollicis and quadriceps femoris muscles was not statistically significantly different between the follicular and luteal phases or among days within either phase --- although for quadriceps femoris muscle, endurance time to exhaustion tended (P=0.07) to be improved during the luteal phase compared to the follicular phase. Studies having similar muscle endurance data with which to compare these results are rare and those that

do exist are contradictory. Moreover, direct muscle endurance performance comparisons of results from the current study with results reported from previous studies are difficult because of an interstudy inconsistency of experimental variables such as in muscle size, type of contraction (e.g., static vs dynamic, electrically stimulated vs voluntary), and contraction intensity. How such exercise model variables interact with varying ovarian hormone levels to affect endurance performance among different subjects from different studies is not well understood. An inability to account for this interaction could be a reason for the diverging observations among previous work. For example, Petrofsky et al., (57) reported that muscle endurance during sustained static handgrip exercise at 40% of MVC to exhaustion was *reduced* during the mid-luteal phase while Sarwar et al., (67) reported that the quadriceps femoris muscle electrically stimulated during static knee extension was less fatiguable (i.e., had *more* endurance) during the mid- and late-luteal phases. Others (17) have reported that different phases of the menstrual cycle have no effect on muscle endurance of the knee extensors and flexors during short-duration, high-intensity, isokinetic contractions.

Due to a lack of uniformity in the exercise endurance performance model selections of previous work and inconsistency of results, the two exercise models in the present study were chosen *because* they involved different muscles of varying sizes and fiber types, different types of voluntary contractions, and varying submaximal exercise contractile forces. Conducting two different muscle endurance exercise performance tests on the same group of women under the identical experimental conditions provides a powerful means with which to determine if cyclic changes in ovarian hormone concentrations alters muscle endurance. Based on the results of the present investigation, it is concluded that muscle endurance is not likely affected by cyclic

changes in ovarian hormones associated with the menstrual cycle.

B. Altitude Exercise Performance During The Menstrual Cycle

1. *Adductor Pollicis and Quadriceps Femoris Muscle Strength*

There was no change in muscle strength of the adductor pollicis muscle and the quadriceps femoris muscle during acute or prolonged exposure to altitude compared to sea level for either the follicular or luteal menstrual cycle phase groups. No change in adductor pollicis strength during acute and chronic altitude exposure (25) or in quadriceps femoris strength during acute altitude exposure (27) compared to baseline sea-level values has also been observed for men. These data indicate that it is unlikely that the periodic fluctuation in ovarian hormone concentrations occurring throughout the course of a normal cycle during altitude acclimatization have any significant influence on muscle strength.

2. *Adductor Pollicis and Quadriceps Femoris Muscle Endurance*

There were no statistically significant main effect differences in endurance time to exhaustion between menstrual cycle phases or environment for the adductor pollicis and quadriceps femoris exercise models. However, endurance time for the luteal group during adductor pollicis testing and the follicular and luteal groups during quadriceps femoris testing tended to be reduced during the first day of altitude exposure (and second day after either the onset of menses or LH surge). For the fifth/sixth and nine/ten testing days within each phase, times to exhaustion at altitude were numerically similar to the same phase test day at sea level (with the exception of day nine/ten of the luteal phase during quadriceps femoris testing). Similar exercise responses of oxygen consumption, percentage of arterial oxygen saturation, and heart rate were measured for the two groups in reference to days at altitude. However, the small

sample sizes and large inter-subject variability --- especially for the luteal phase group for both exercise models --- precludes making a final conclusion as to whether differences in menstrual cycle phase affect intermittent static contraction or dynamic contraction muscle endurance performance at altitude.

C. Gender Comparisons

1. *Adductor Pollicis Muscle Strength and Submaximal Exercise Performance at Sea Level*

At sea level, adductor pollicis strength of women was less than that of men (measured in a previous study using a similar experimental design (25). Based on previous reports comparing men and women using static small muscle contractions (42,56), such a result was expected. Also expected was our observation that endurance time to exhaustion was longer for women than men. Previous gender comparisons in which men and women exercised at the same *relative* percentage of maximal contractile force (as in the current study) had indicated that muscle endurance was significantly longer for women than men (47,50,56,79). However, complicating the interpretation of these studies relates to the fact that the stronger men were using a submaximal contractions having a greater *absolute* force and thus a proportionally higher intramuscular pressure and increased muscle ischemia (70) than women. Thus the shorter endurance times to exhaustion for men may relate simply to exacerbation of fatigue processes by diminished local blood flow and oxygen delivery rather than intrinsic gender differences in specific fatigue processes, per se.

To compare endurance times to exhaustion of men and women under exercise conditions in which potential differences in intramuscular pressure and local muscle ischemia would be

minimized, we matched men (25) and women on strength. Doing so also caused matching of the relative and absolute submaximal intermittent contractile forces and likely similar degrees of intramuscular pressure and local muscle ischemia for men and women. Our findings clearly indicate that women have a markedly longer endurance time to exhaustion. To our knowledge, this is the first demonstration of different endurance times between men and women contracting at both the same absolute force and relative percentage of strength.

The greater endurance performance of women compared to men has been proposed to involve a lower glycolytic to beta-oxidation potential in skeletal muscle in women than in men (30,54), a decreased rate of muscle glycogen depletion and a lower blood lactate concentration during dynamic leg exercise at similar relative work rates (75), and a larger proportion of active muscle volume occupied by slow-twitch fibers (a consequence of women having a smaller, fast-twitch fiber cross-sectional area (54). Leg extensor endurance performance during sustained static contractions in untrained individuals is, however, not always directly related to percentage of slow-twitch muscle fibers (48).

Explaining the greater adductor pollicis muscle endurance of women than men in the current study in terms of possible gender differences in glycolytic relative to oxidative metabolism and in the ratio of slow-to-fast twitch fiber area must be considered with caution since the proportion of slow-fatiguing type I muscle fibers for both genders is much greater for the adductor pollicis (mean: 80% (63)) than for the leg extensor muscles (mean: 50% (48,54)). A similar predominance of type I fibers in the adductor pollicis muscle for both men and women would tend to minimize potential gender differences in muscle endurance due to differences in fiber type. Moreover, we observed markedly lower adductor pollicis strength for men than

women after only one minute (a total of six contractions), a difference unlikely to relate to muscle glycogen depletion.

2. *Adductor Pollicis Muscle Strength and Submaximal Exercise Performance at Altitude*

Both men (25) and women maintained their sea level strength levels on acute exposure to altitude. However, endurance time to exhaustion in women --- in sharp contrast to men --- was similar at sea level and altitude. In men at altitude, there was a decrease in endurance time to exhaustion. The reason for the adductor pollicis muscle endurance difference between men and women at altitude is poorly understood. For reasons given above for sea level exercise performance, it is difficult to implicate gender differences in oxidative metabolism and muscle fiber type cross-sectional areas as responsible for the gender differences in endurance performance at altitude. Moreover, because the magnitude of the performance difference between men and women was widened --- and not merely maintained --- at altitude compared to sea level suggests that the beneficial factor(s) responsible for the gender difference in performance at sea level may have an increased impact for women during exposure to altitude. More research is clearly warranted to define the precise mechanism(s) responsible for the adductor pollicis muscle endurance difference between men and women at sea level and altitude.

3. *Quadriceps Femoris Muscle Strength and Submaximal Exercise Performance at Sea Level and Altitude*

In the present study, mean values for rested MVC force (i.e., muscle strength) were nearly identical for men and women at sea level and altitude. Unlike the adductor pollicis analysis presented above, similar values for quadriceps femoris strength for men and women were

coincidental. Unfortunately, previous data on men (25,27) showed that endurance time to exhaustion during one-leg knee extension dynamic exercise is poorly related to rested MVC force ($r = 0.16$, $P > 0.40$), but is highly related to one-leg peak oxygen uptake (VO_{2peak}, $r = 0.75$, $P < 0.01$). However, in the present study on women, few one-leg VO_{2peak} measurements were performed and the ones that were performed did not include the women who subsequently participated in the altitude phase (see **Experimental Methods Section C.1.**). Without such data --- which would have been the performance variable used to match men and women --- it is difficult to accurately assess gender differences in knee extension endurance times. In other words, the reduced endurance time to exhaustion of women compared to men observed in the present study at sea level ($P < 0.05$) and, to a lessor extent at altitude ($P > 0.05$), may be related to the women exercising at a higher percentage of their one-leg VO_{2peak}, i.e. a higher relative exercise intensity, than men. This postulate seems likely, given the greater endurance performance of the adductor pollicis muscle in women compared to men when the relative and absolute submaximal intermittent contractile forces were equalized.

It is important to emphasize that with the dynamic knee extension exercise model, rested MVC force, percentage of rested force used during dynamic exercise, and the remaining MVC at exhaustion --- as well as the percentage of VO_{2peak} used for submaximal exercise --- are important dependent factors that can act individually or collectively to significantly affect endurance time to exhaustion (45). Closer inspection of the data presented in **TABLE 10** illustrates the implication of this statement. While men and women had nearly identical rested MVC force at sea level and altitude, the force used during dynamic submaximal exercise had a tendency ($P > 0.05$) to be higher for women than for men. A higher relative percentage of rested

MVC force used during submaximal exercise would accelerate the rate of muscle fatigue and result in a shorter endurance time (47). In addition, remaining MVC force at exhaustion was significantly higher for women than men ($P < 0.05$) which would also reduce endurance time to exhaustion (see **FIGURE 2**). The reason for the consistently higher remaining MVC force in women compared to men is not known. However, because there was no difference in inactive left leg MVC force measured just prior to and at the moment of exhaustion from dynamic exercise of the active right leg during any of the exercise sessions, a general attenuation of central motor drive due to reduced subject motivation can be ruled out (27).

A direct gender comparison of quadriceps femoris endurance performance at sea level and altitude is difficult to realize since men and women may have exercised at different relative percentages of VO_{2peak}. However, since each man and women performed dynamic knee extension exercise at the same respective dynamic force, velocity, dynamic work rate, and energy requirement at altitude as at sea level, intra-individual changes in endurance performance due to altitude exposure can be determined. Using this approach, we calculated that women compared to men tended to have less of a decrement on exposure to altitude (mean: -22% vs -56%, respectively). It is interesting that on exposure to altitude all eight men, but only eight of the 11 women had a reduction in endurance time (three in the follicular group improved) and that the variation of individual changes ($\pm$ 1 SD) in endurance time was much less for men (-35% to -77%) than for women (+100% to -74%). Exactly why women had a tendency not to have as large a decline in exercise performance as men or why there was greater intra-individual variation upon exposure to altitude for women than men requires further study.

CONCLUSIONS

The experimental design allowed skeletal muscle strength and endurance time to exhaustion to be measured repeatedly during the follicular and luteal phases of healthy, eumenorrhic women at sea level and altitude. The two exercise performance models used --- the adductor pollicis intermittent static and the quadriceps femoris dynamic contraction exercise models --- have relatively minor intra-individual test-retest variability, are sensitive to experimental interventions, and provide multiple, quantifiable performance indexes (e.g., muscle strength and muscle endurance). Study emphasis was on determining if muscle strength and muscle endurance was affected by cyclic variations in the hormonal milieu associated with the menstrual cycle at sea level and altitude, and to determine if muscle function of women differs from that of men (historical controls) at sea level and during acute exposure to altitude.

We determined that muscle strength of the adductor pollicis muscle and the larger quadriceps femoris muscle was not meaningfully influenced by the periodic fluctuation in ovarian hormone concentrations occurring throughout the course of a normal cycle at sea level and during altitude acclimatization. There were no statistically significant differences in endurance time to exhaustion between menstrual cycle phases or environments for either the adductor pollicis or quadriceps femoris exercise models. Nevertheless, endurance times for the luteal group during adductor pollicis exercise test and for the follicular and luteal groups during quadriceps femoris exercise test tended to be reduced during initial altitude exposure. Small sample sizes and inter-subject variability, however, precludes making definitive conclusions as to whether differences in menstrual cycle phase affect muscle endurance performance at altitude.

Women compared to men had a markedly longer endurance time to exhaustion at the

same absolute and relative contractile forces during adductor pollicis submaximal intermittent exercise. The exact mechanism responsible for muscle endurance superiority does not likely relate to previously proposed mechanisms involving gender differences in glycolytic relative to oxidative metabolism and in the ratio of slow-to-fast twitch fiber area. A markedly higher adductor pollicis strength for women compared to men after only one minute (a total of six contractions) suggests the endurance performance difference was unlikely related to different rates of muscle glycogen depletion between men and women. Moreover, the known predominance of type I fibers (80% of active fibers) in the adductor pollicis muscle for both men and women would tend to minimize potential gender differences in muscle endurance due to gender differences in fiber type.

Both men and women maintained their sea level strength levels on acute exposure to altitude. However, endurance time to exhaustion in women for both exercise performance models --- in sharp contrast to men --- was much better maintained at altitude compared to sea level. In other words, women compared to men have a lesser endurance performance decrement on exposure to altitude, and the lesser decrement is independent of menstrual cycle phase. More research is clearly warranted to define the precise mechanism(s) responsible for the muscle endurance performance difference between men and women on exposure to altitude.

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APPENDICES

APPENDIX A: TABLES

	TABLE 1. **Women Available For Various Comparisons at Sea Level and Altitude During Adductor Pollicis and Knee Extension Exercise Testing.**						
	Adductor Pollicis Exercise Comparisons				**Knee Extension Exercise Comparisons**		
Sub #	**SL[1]**	**SL to ALT[2]**	**Men[3]**	**Men[4]**	**SL[5]**	**SL to ALT[6]**	**Men[7]**
A	X				X		
B	X	X,F	X	X	X	X,F	X
C	X	X,F	X	X	X	X,F	X
D				X			
E					X	X,F	X
F	X	X,L		X	X	X,L	X
G	X	X,F	X	X	X	X,F	X
H	X						
I		X,F	X				
J		X,F	X			X,F	X
K		X,F	X	X		X,F	X
L						X,F	X
M		X,F	X			X,F	X
N	X	X,L			X	X,L	X
O	X	X,F	X	X			
P	X			X			
Q		X,L				X,L	X
R	X	X,L		X			
S	X	X,L					

X = Subject was used for this comparison. **1** = Adductor pollicis data were collected at sea level (SL) for both the follicular and luteal phases. **2** = Adductor pollicis data were collected at SL and altitude (ALT). SL to ALT comparisons were made during the same phase --- follicular (F) or luteal (L) --- of the menstrual cycle. **3** = Comparison of adductor pollicis data of women and men (25) during similar acute exposures to altitude. Only women in the follicular group were used. **4** = Comparison of muscle endurance of women who were matched to men (25) on static adductor pollicis strength at sea level. **5** = Knee extension data were collected at SL for both the F and L phases. **6** = Knee extension data were collected at SL and ALT. SL to ALT comparisons were made during the same phase, F or L, of the menstrual cycle. **7** = Comparison to men (n=8, from ref (27)) of maximal and submaximal knee extension exercise performance indeces during acute exposure to altitude. Women were in the second day of the follicular (n=8) or luteal (n=3) phase.

TABLE 2. Serum Values ($pg \cdot ml^{-1}$) for Estradiol and Progesterone During the Follicular and Luteal Phases at Sea Level and Altitude.

	Sea Level, Follicular			Sea Level, Luteal		
Day	**n**	**E_2**	**P_4**	**n**	**E_2**	**P_4**
3	18	51 ± 46	0.8 ± 0.4	13	108 ± 37*	3.6 ± 1.9*
10	19	50 ± 12	0.5 ± 0.1	12	90 ± 37*	7.0 ± 4.9*

Values are means $\pm$ SD, * $P < 0.05$, follicular vs luteal phase.
E_2 = estradiol, P_4 = progesterone

	Altitude, Follicular			Altitude, Luteal		
Day	**n**	**E_2**	**P_4**	**n**	**E_2**	**P_4**
3	11	59 ± 49	0.6 ± 0.2	5	102 ± 31	2.3 ± 1.3*
6	11	79 ± 76	0.6 ± 0.1	5	150 ± 94	5.2 ± 3.4*
9	11	80 ± 59	0.8 ± 0.3	5	83 ± 39	5.7 ± 6.1*
10	10	73 ± 31	0.6 ± 0.4	5	73 ± 46	7.0 ± 7.6*

Values are means $\pm$ SD, * $P < 0.05$, follicular vs luteal phase.
E_2 = estradiol, P_4 = progesterone

TABLE 3. Adductor Pollicis Maximal Voluntary Contractile (MVC) Force and Endurance Time to Exhaustion During the Follicular and Luteal Phases of the Same Subjects at Sea Level.

Maximal Static Voluntary Contractile Force (kgs)					
Follicular Phase			Luteal Phase		
Day 1	Day 5	Day 9	Day 1	Day 5	Day 9
10.9 ± 0.6	11.3 ± 0.5	11.5 ± 0.8	11.1 ± 0.5	11.7 ± 0.6	11.0 ± 0.5

Endurance Time to Exhaustion (mins)					
Follicular Phase			Luteal Phase		
Day 1	Day 5	Day 9	Day 1	Day 5	Day 9
18.6 ± 3.4	17.7 ± 1.8	16.9 ± 3.0	18.1 ± 3.4	14.8 ± 3.0	16.9 ± 2.7

n = 11; Values are means ± SE

TABLE 4. Quadriceps Femoris Maximal Voluntary Contractile (MVC) Force, Endurance Time to Exhaustion, Dynamic Knee Extension Force and Remaining MVC Force (both as a percentage of rested MVC Force), and Steady-State Heart Rate and Oxygen Uptake During the Follicular and Luteal Phases of the Same Subjects at Sea Level.

	Follicular Phase			Luteal Phase		
	Day 1	**Day 5**	**Day 9**	**Day 1**	**Day 5**	**Day 9**
Rested MVC Force (kgs)	55.6 ± 3.2	54.9 ± 3.1	53.7 ± 2.4	57.2 ± 3.5	56.2 ± 2.9	54.0 ± 2.3
Endurance Time (min)	18.0 ± 3.3	18.3 ± 3.4	20.2 ± 2.9	25.6 ± 4.6	24.1 ± 4.6	24.9 ± 4.5
Dynamic Force (%Rested MVC)	19.2 ± 1.6	19.1 ± 1.6	18.7 ± 1.6	20.0 ± 1.9	18.7 ± 1.8	19.2 ± 2.0
RemainingMVC (%Rested MVC)	60.4 ± 6	57.5 ± 5	56.7 ± 5	59.7 ± 6	62.4 ± 6	62.8 ± 6
O_2 Uptake (ml •min^{-1})	709 ± 37	717 ± 57	733 ± 53	767 ± 71	747 ± 40	673 ± 39
Heart Rate (beats •min^{-1})	115 ± 5	114 ± 5	111 ± 5	130 ± 6*	124 ± 5	120 ± 5

n = 7; Values are means ± SE.
*P < 0.01 from follicular days 1,5, and 9
Note: Follicular vs Luteal statistical main effect for endurance time is p = 0.07

TABLE 5. Adductor Pollicis Maximal Voluntary Contractile (MVC) Force and Endurance Time to Exhaustion For Follicular and Luteal Groups at Sea Level and Altitude.

	Maximal Static Voluntary Contractile Force (kgs)					
	Follicular Group (n = 8)			Luteal Group (n = 5)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	11.6 ± 0.4	11.4 ± 0.4	11.5 ± 0.6	10.9 ± 0.6	12.0 ± 0.8	11.8 ± 0.6
ALT	12.6 ± 0.5	12.0 ± 0.7	12.2 ± 0.8	12.2 ± 1.0	12.2 ± 1.0	12.8 ± 1.2

	Endurance Time to Exhaustion (mins)					
	Follicular Group (n = 8)			Luteal Group (n = 5)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	13.4 ± 1.6	15.8 ± 1.4	18.3 ± 3.6	23.0 ± 6.6	14.4 ± 5.5	18.0 ± 5.2
ALT	14.6 ± 2.2	18.6 ± 3.3	21.1 ± 3.2	14.6 ± 2.5	17.4 ± 1.7	19.3 ± 2.5

SL = sea level, ALT = altitude. Values are means ± SE

TABLE 6. Quadriceps Femoris Maximal Voluntary Contractile (MVC) Force and Endurance Time to Exhaustion For Follicular and Luteal Groups at Sea Level and Altitude.

	Maximal Static Voluntary Contractile Force (kgs)					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	58.5 ± 5.0	57.6 ± 4.7	55.8 ± 4.7	57.6 ± 4.2	59.9 ± 3.7	58.5 ± 6.9
ALT	60.8 ± 5.4	58.5 ± 5.5	59.4 ± 6.6	57.6 ± 10.0	59.4 ± 6.3	59.4 ± 8.4

	Endurance Time to Exhaustion (mins)					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	20.0 ± 4.0	20.1 ± 3.6	21.7 ± 3.5	27.4 ± 8.8	28.0 ± 6.1	21.0 ± 5.5
ALT	13.0 ± 3.0	19.3 ± 5.8	19.7 ± 4.5	16.0 ± 5.3	29.3 ± 4.0	46.7 ± 21.7

	Percentage of Rested MVC Remaining at Exhaustion					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	60.1 ± 4	55.9 ± 4	62.4 ± 8	72.3 ± 10	72.0 ± 8	65.0 ± 10
ALT	54.9 ± 4	55.0 ± 5	57.1 ± 4	61.8 ± 4	69.7 ± 4	50.5 ± 8

SL = sea level, ALT = altitude. Values are means ± SE

TABLE 7. Quadriceps Femoris Dynamic Knee Extension Force, Oxygen Consumption and Arterial Oxygen Saturation For Follicular and Luteal Groups at Sea Level and Altitude.

	Percentage of Rested MVC Force Used During Dynamic Knee Extension					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	20.6 ± 1.3	21.3 ± 2.3	21.2 ± 1.8	18.2 ± 4.6	17.6 ± 4.1	19.7 ± 4.4
ALT	20.6 ± 1.7	21.9 ± 2.0	22.5 ± 2.1	19.8 ± 2.3	19.4 ± 3.6	17.6 ± 2.8

	Oxygen Consumption During Dynamic Knee Extension (ml •min^{-1})					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	703 ± 23	723 ± 42	710 ± 43	685 ± 106	706 ± 80	631 ± 72
ALT	736 ± 37	729 ± 25	762 ± 40	669 ± 87	829 ± 185	698 ± 105

	Percentage Arterial Oxygen Saturation During Dynamic Knee Extension					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	97 ± 0.2	98 ± 0.2	97 ± 0.4	98 ± 0.3	97 ± 0.6	97 ± 0.3
ALT	88 ± 1.3*	90 ± 0.9*	90 ± 0.6*	86 ± 0.3*	88 ± 1.5*	88 ± 0.9*

	Heart Rate During Dynamic Knee Extension (beats •min^{-1})					
	Follicular Group (n = 8)			Luteal Group (n = 3)		
	Days 1-2	Days 5-6	Days 9-10	Days 1-2	Days 5-6	Days 9-10
SL	121 ± 6	117 ± 7	114 ± 7	124 ± 9	116 ± 8	112 ± 9
ALT	129 ± 11	130 ± 5	131 ± 8*	133 ± 0	132 ± 5	134 ± 1

SL = sea level, ALT = altitude. Values are means ± SE. *P <0.05 from sea level

TABLE 8. Adductor Pollicis Maximal Voluntary Contractile (MVC) Force and Endurance Time to Exhaustion For Men and Women at Sea Level and Altitude.

	Men (n = 8)*		Women (n = 8)	
	Sea Level	Altitude	Sea Level	Altitude
MVC Force (kg)	14.2 ± 0.6^{a}	15.4 ± 0.5^{a}	11.6 ± 0.4	12.6 ± 0.5
Endurance (min)	7.4 ± 0.6	5.1 ± 0.5^{c}	13.4 ± 1.6^{b}	14.6 ± 2.2^{b}

*From reference (25). Adductor pollicis testing device and procedures, and length of altitude exposure were nearly identical to the present study. a = Greater rested MVC force than women ($P < 0.05$), b = Longer endurance time to exhaustion than men ($P < 0.05$), c = Reduced from sea level (- 31%, $P < 0.05$).

TABLE 9. Adductor Pollicis Endurance Time to Exhaustion For Men and Women Matched on Maximal Voluntary Contractile (MVC) Force

	Men (n = 9)*	Women (n = 9)
MVC Force (kg)	14.2 ± 0.4	13.5 ± 0.4
Endurance (min)	7.9 ± 0.7	14.7 ± 1.2[a]

*From reference (25). Adductor pollicis testing device and procedures, were identical to the present study.
a = Longer endurance time to exhaustion than men ($P < 0.05$)

TABLE 10. Comparison of Men[a] and Women During Knee Extension Exercise at Sea Level and Altitude.

	Men (n = 8)[a]		Women (n = 11)[b]	
	Sea Level	**Altitude**	**Sea Level**	**Altitude**
Rested MVC Force (kg)	59.0 ± 3.0	58.1 ± 3.0	58.0 ± 3.6	59.9 ± 4.
Dynamic Force (% rested MVC)	18.0 ± 3.0	18.0 ± 3.0	19.9 ± 1.5	20.4 ± 1.3
Dynamic Work Rate (watts)	21.0 ± 3	21.0 ± 3	17.8 ± 1	18.4 ± 1
Endurance Time (mins)	43.0 ± 7	19.5 ± 5[c]	22.0 ± 4[d]	13.8 ± 3[e]
Remaining MVC at Exhaustion (% rested MVC)	47.0 ± 3	49.0 ± 3	63.4 ± 4[f]	56.7 ± 3[f]
Oxygen Uptake (ml $\bullet$min^{-1})	818 ± 45	832 ± 52	698 ± 30	718 ± 34
% Sea Level, 1-leg VO_{2peak}	79.0 ± 2	87.2 ± 2[g]	???	???
Heart Rate (beats $\bullet$min^{-1})	106 ± 4	124 ± 7[g]	122 ± 5[h]	130 ± 4
Arterial Saturation (%)	97.1 ± 0.2	83.6 ± 1.3[i]	97.5 ± 0.2	87.5 ± 1.0[i]

Values are means ± S.E. a = From reference (27). b = Current study data. Combined follicular and luteal groups during the first day of their respective phase at sea level and during the first day at altitude. c = Decreased ($P < 0.01$) from sea level. Mean reduction from sea level for men was 56 ± 7%. d = Sea Level value of women lower ($P < 0.05$) than that of men. e = No difference ($P = 0.08$) from women at sea level. Mean reduction from sea level for women was 22 ± 16%. f = Higher ($P < 0.05$) then respective value for men. g = Increased ($P < 0.01$) from sea level. h = Higher ($P < 0.05$) than sea level value for men. i = Decreased ($P < 0.01$) from sea level.

APPENDIX B: FIGURES

FIGURE 1
ADDUCTOR POLLICIS EXERCISE MODEL

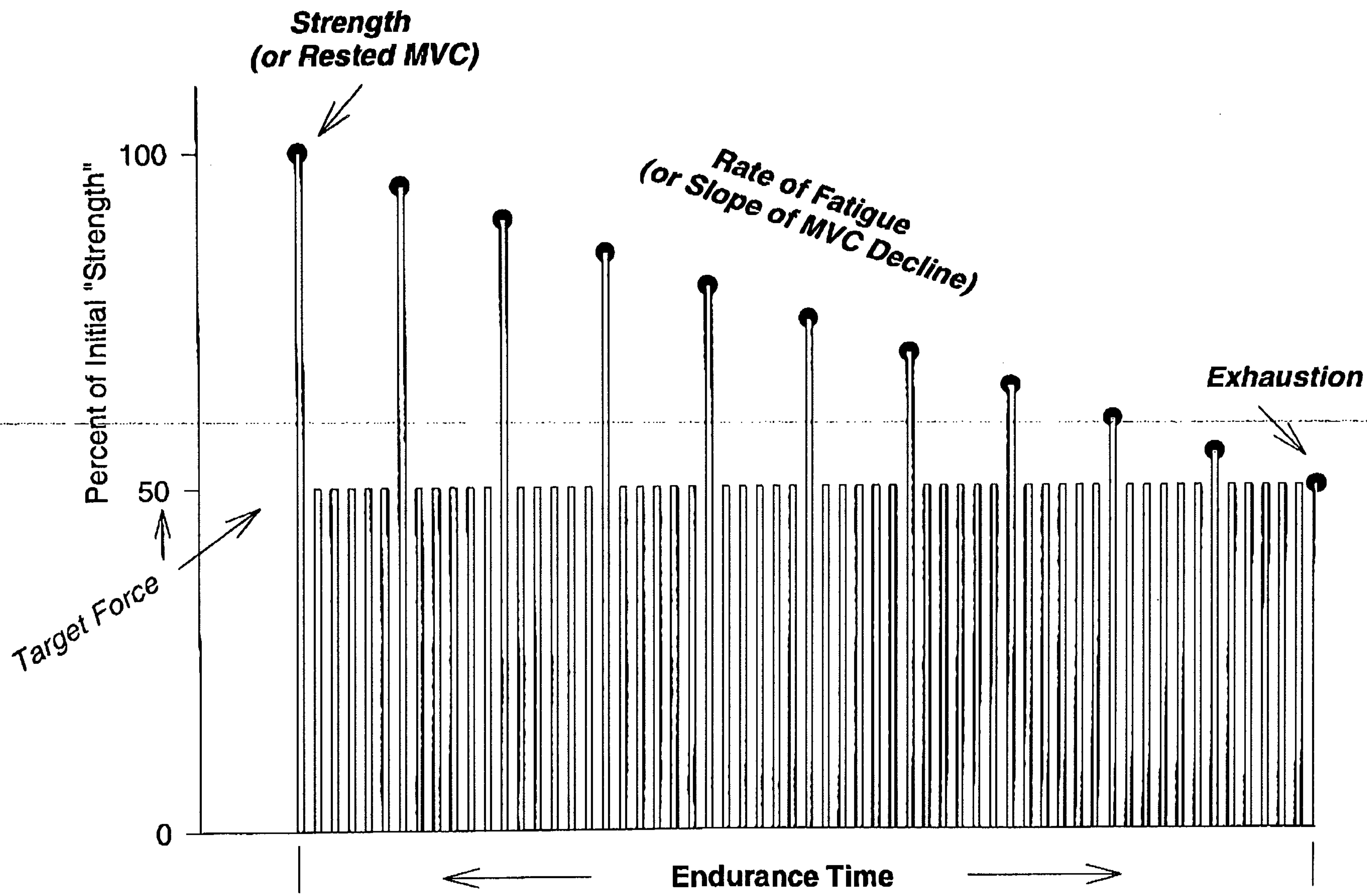


FIGURE 2
QUADRICEPS FEMORIS EXERCISE MODEL

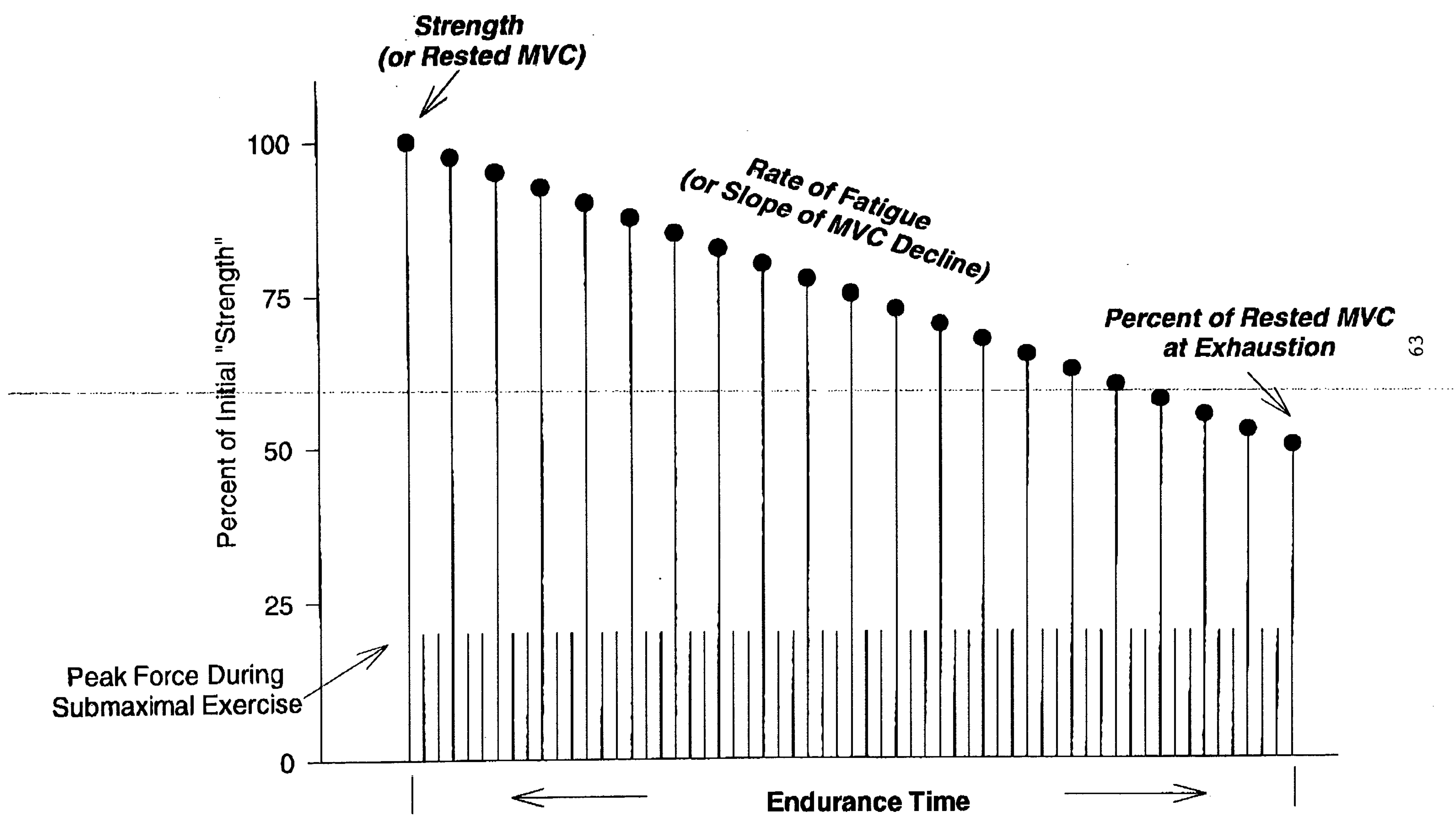
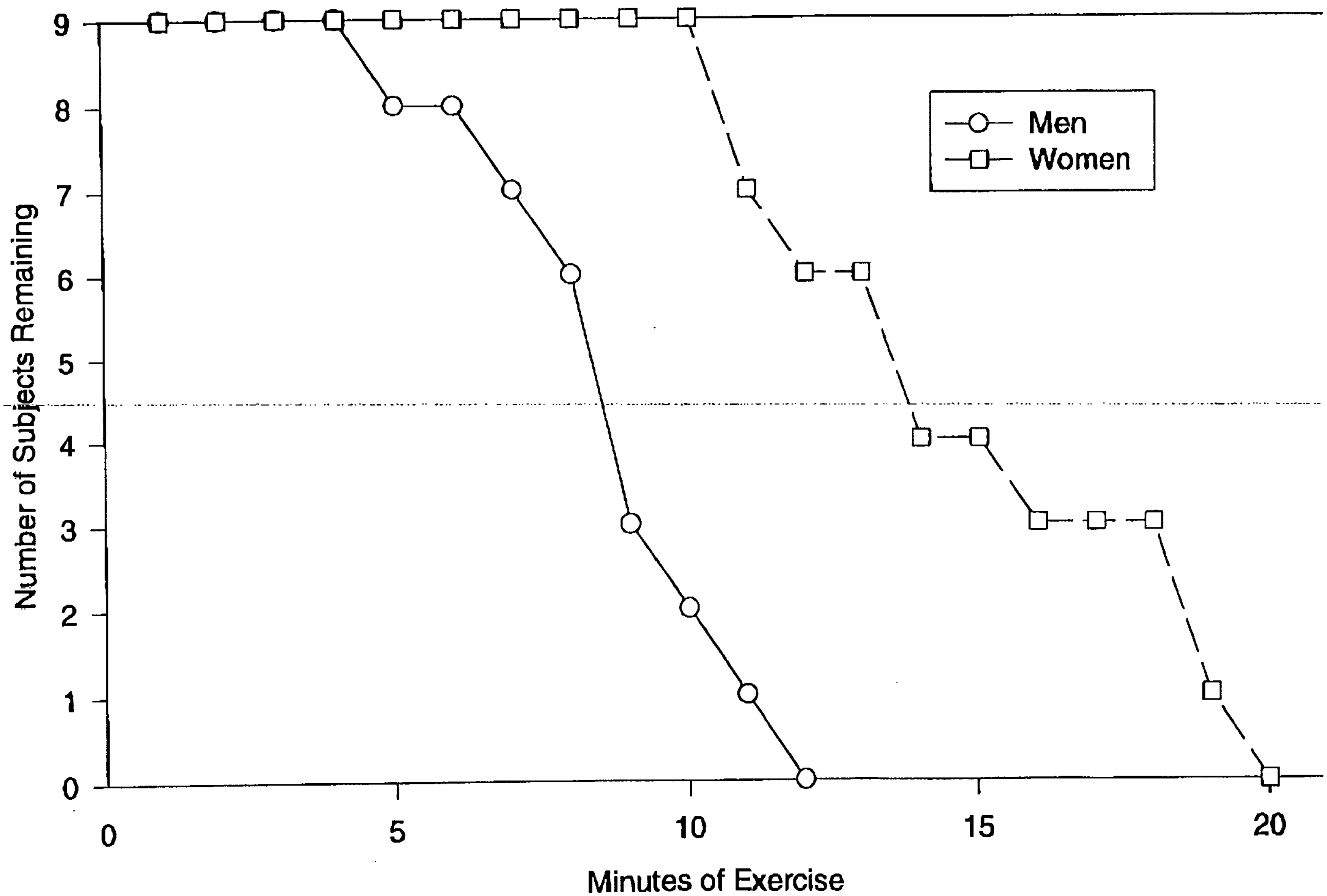


FIGURE 3
NUMBER OF MEN AND WOMEN ABLE TO CONTINUE AFTER EACH MINUTE OF EXERCISE



APPENDIX C
FIGURE LEGENDS

Figure 1: Schematic of model for measuring progressive fatigue of intermittent static contractions. "*Strength*" is the highest maximal voluntary static contraction (MVC) force of rested muscle obtained at the start of exercise. The "target force"of submaximal contractions is set to a given percentage of strength. The durations of the target force contraction and the rest period following each contraction can each be adjusted to obtain any duty cycle. A MVC also is performed at the end of a specified time period or number of target-force contractions. "*Rate of Fatigue*" is defined as the rate of decline of MVC force resulting from the target force contractions. "*Exhaustion*" occurs when MVC force falls to the target force value or the target force cannot be maintained for a specified duration. "*Endurance Time*" is the time interval from the start of exercise to the exhaustion point. In the figure, the target force equals 50% of strength, both the MVC and target force contractions and rest periods last 5 sec (i.e., duty cycle = 0.5), and a MVC is performed at the end of each min (or every sixth contraction). Modified from Bigland-Ritchie and Woods (6).

Figure 2: Schematic of dynamic knee extension fatigue model. "*Strength*" or maximal voluntary static contraction (MVC) force of rested muscle is the highest MVC force obtained prior to the start of dynamic exercise. Peak force during each dynamic knee extension is the product of the amount of weight lifted and the speed with which the weight is displaced. Also, MVCs are repeated at specific points in time (every 4 min) during dynamic exercise. "*Rate of Fatigue*" is defined as the rate of decline of MVC force resulting from dynamic knee extension exercise. "*Exhaustion*" occurs when an individual is unable for three consecutive contractions to maintain

the rate of knee extension and/or the distance of ankle movement. In the figure, peak force during each submaximal contraction equals 20% of MVC force of rested muscle, a MVC is performed periodically throughout dynamic knee extension, and, at exhaustion, the percent MVC force equals 50% that of rested muscle. In contrast to the static contraction fatigue model depicted in Figure 1, the point of exhaustion for dynamic knee extension occurs with MVC force remaining substantially above the level of peak force during submaximal contractions, a consequence of the classical force-velocity relationship. That is, more force can be provided by a static contraction compared to a dynamic contraction at any given angle.

Figure 3: This graph shows the number of men (25) and women --- who were matched on adductor pollicis maximal voluntary contraction (MVC) force --- remaining after each minute of adductor pollicis intermittent static exercise. All men were able to complete 4 min of static contractions at 50% MVC force but none could exercise beyond min 12. All women were able to complete 10 min of static contraction at 50% MVC force. By min 12, only 3 of 9 women reached exhaustion.

APPENDIX D

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APPENDIX E

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APPENDIX F

LIST OF PERSONNEL RECEIVING PAY

Mr. Eric Lammi, Personal Contractor